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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/505,191	06/24/2005	Jeffrey P. Erickson	AIB-09206	5158

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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,191	ERICKSON, JEFFREY P.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-13,15-21,23,27-29,33 and 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-13,15-21,23,27-29,33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 11/30/2009 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1, 6-13, 15-21, 23, 27-29, 33-34 are pending and under consideration. Claims 2-5, 14, 22, 24-26, 30-32, 35-40 are canceled.

The declaration submitted 11/30/2009 has been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6-13, 15-21, 23, 27-29, 33-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic caprine comprising a bSP30a or a bSP30b promoter, wherein said promoter is operably linked to an exogenous nucleic acid encoding at least one transgenic polypeptide, wherein said polypeptide is produced in said caprine's saliva, does not reasonably provide enablement for a transgenic caprinel comprising all bovine salivary gland promoters other than the bSP30a or bSP30b promoter . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a transgenic caprine whose genome comprises an exogenous nucleic acid encoding at least one transgenic polypeptide, said nucleic acid operably linked to a salivary gland-specific cis-acting 5' transcription control region, wherein said control region comprises a bovine salivary gland protein promoter. Independent claim 20 is directed to a

method, comprising: a) providing; i) a transgenic caprine whose genome comprises an exogenous nucleic acid encoding at least one transgenic polypeptide, said nucleic acid operably linked to a salivary gland-specific cis-acting 5' transcriptional control region, said caprine capable of producing saliva, wherein said polypeptide is produced in said saliva and is collected from a salivary gland duct; ii) a flexible tubing to collect said saliva; b) making a surgical incision in said salivary gland duct; and c) cannulating said duct with said tubing. Independent claim 29 is directed to a method, comprising: a) providing; i) a first DNA sequence comprising 5' cis-acting expression signals, said first DNA sequence being derived from a first salivary gland secretory protein gene, said first gene comprising a bovine salivary gland protein promoter ii) a second DNA sequence encoding a polypeptide of interest and a region encoding an operable secretion signal, said secretion signal being derived from a second salivary gland secretory protein gene; iii) a third DNA sequence comprising termination and 3' regulatory signals, said third DNA sequence being derived from a third salivary gland secretory protein gene, wherein said first, second, and third salivary gland secretory protein genes are not necessarily different; b) joining said first, second, third DNA sequences in operable linkage effective for salivary gland expression and saliva-specific expression of said polypeptide of interest to create a transgene construct; c) cloning said transgene construct to produce a vector; d) microinjecting said vector into a caprine embryo to produce a transgenic caprine whose genome comprises a transgenic polypeptide transgene capable of engendering expression of said polypeptide in saliva of said caprine.

The specification discusses that salivary gland and saliva specific regulatory elements are necessary to achieve saliva specific expression of a polypeptide of interest in a transgenic non-human animal including a caprine (See pages 26-28, 33 of the specification). The declaration submitted on 10/01/2007 by Jeffrey Erickson discloses a transgenic goat expressing

the human serum albumin protein within its salivary gland was successfully created. In particular, a plasmid vector with a bovine salivary protein promoter (bSP30a) ligated to a human serum albumin protein, thereby places a bSP signal peptide sequence, a mature protein sequence, and a Poly A termination sequence all downstream of a bSP promoter sequence. The transgenic doe was birthed that has been shown to be transgenic with transfected gene consisting of the bSP30a promoter and the human serum albumin gene. Secretion of the human serum albumin into the transgenic doe's saliva shows that the transgene is functional and expressed in the salivary gland. However, the guidance provided by the specification and the declaration does not provide guidance for a Tg caprine lacking said particular bSP30a salivary gland specific promoter for the creation of transgenic caprine as embraced by the claims. Moreover, the guidance provided by the specification is general as it does not even disclose which saliva regulatory elements could be used to create a transgenic caprine embraced by the claims. Therefore the specification has failed to provide the skilled artisan with adequate guidance to make a transgenic caprine embraced by the claims. Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to make and use the invention as claimed without a reasonable expectation of success.

The claims embrace a transgenic caprine that express and produce a transgenic polypeptide in saliva. The specification has discussed that saliva specific regulatory elements are necessary to achieve expression of a polypeptide of interest in saliva of a transgenic non-human mammal. See pages 26-29 of the specification. However, the guidance provided by the specification with respect to use of saliva specific regulatory elements was general and did not specifically relate to use of any particular regulatory sequence. Moreover, the specification while suggesting that certain regulatory elements (PSP and B1-Ips genes) (p 27-28) could be used failed to disclose the actual nucleotide sequences of such elements, which could direct a

high level of transgene expression in saliva. This is an important point because the prior art has set forth that regulatory sequences of genes expressed in the cells of salivary gland are basically undeveloped and failed to direct high levels of polypeptide expression. See Samuelson (Annu. Rev. Phys., 1996, 58: 209-229 (IDS)), for example on page 217, which discussed the limitations of using the “known” promoter sequence of the parotid secretory protein (PSP) gene. The working examples (see pages 81-101 of the specification) discussed the creation of separate transgenic cows that expressed prothrombin and fibrinogen respectively in their saliva. However, the working examples failed to disclose which saliva regulatory elements were used in the creation the transgenic caprine. The specification as a whole has not even identified or provided the regulatory elements necessary to practice the claimed invention. A mere statement that saliva regulatory elements existed and could be used is not sufficient to enable the claims as directed to a transgenic caprine expressing transgenic polypeptides in saliva. As discussed in the previous office actions, this is an important point because the prior art has set forth that regulatory sequences of genes expressed in the cells of salivary gland are basically undeveloped and failed to direct high levels of polypeptide expression. See Samuelson (Annu. Rev. Phys., 1996, 58: 209-229 (IDS)), for example on page 217, which discussed the limitations of using the "known" promoter sequence of the parotid secretory protein (PSP) gene. Also, Samuelson provided an extensive review of the limitations of known salivary gland promoters. See throughout Samuelson. For example, the art teaches that parotid-specific transgene expression requires an upstream cis-regulatory domain, namely the parotid control region, and this parotid control region functions with a heterologous promoter and is indispensable for achieving transgene expression and deletion of specific regions results in ectopic gene expression and the inducible expression of the transgene expression in transgenic mice decreases over 30-fold (abstract) (Tu et al, Gene Expr, 3(3): 289-305, 1993

(IDS)). Moreover, the specification and the declaration teach for a creation of a transgenic caprine salivary gland and saliva specific regulatory elements are necessary to achieve saliva specific expression of a polypeptide of interest in a transgenic caprine in particular, a bovine salivary protein promoter (bSP30a) ligated to a human serum albumin protein, thereby places a bSP signal peptide sequence, a mature protein sequence, and a Poly A termination sequence all downstream of a bSP promoter sequence. In this case, it is unpredictable to make a transgenic caprine lacking said regulatory elements as embraced by the claims other than the transgenic caprine as described in the declaration with the described regulatory elements for transgene expression in the salivary gland of the transgenic caprine. Since it would require undue experimentation to identify other bovine salivary glad promoter regions, other than the bPSP30a or bSP30b promoter able to exhibit the claimed functionality, it would require undue experimentation to make and use of the invention as claimed.

Given, the lack of guidance and absence of working examples provided by the specification correlating to creation of a transgenic caprine, other than a transgenic caprine utilizing saliva specific bSP30a or bSP30b promoter necessary to achieve saliva specific expression of a polypeptide of interest in a transgenic caprine in particular, a bovine salivary protein promoter (bSP30a) ligated to a transgene, thereby places a bSP signal peptide sequence, a mature protein sequence, and a Poly A termination sequence all downstream of a bSP promoter sequence, the unpredictability of lacking said saliva regulatory elements, it would have required undue experimentation for the skilled artisan to practice the claimed invention.

Applicants argue that have amended the claims to recite "a bovine salivary gland protein promoter". See, Applicants' Specification, pg 33, in view of previously submitted Erickson Declaration and The Second Wheeler Declaration (infra). The Applicants find that the Examiner has admitted that such an embodiment is enabled: ... the specification, which being enabling for

a transgenic goat comprising a bSP30a or a bSP30b promoter, wherein said promoter is operably linked to an exogenous nucleic acid encoding at least one transgenic polypeptide ... Office Action, pg. 2, and fulfills the statutory requirements for a genus claim: For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. The Applicants submit that the Erickson Declaration provides the necessary 'representative examples' to support a bovine salivary gland protein genus. The Examiner is respectfully reminded that The Erickson Declaration provided data showing that a recombinant protein was secreted into caprine saliva using either a bSP30A or a bSP30B promoter. For example, in a small genus (i.e., for example, a genus of bovine salivary gland protein promoters), coupled with a lack of undue experimentation, current patent law suggests that a relatively small number of examples are sufficient to establish the genus. Further, the Applicants submit that the specification does provide "a statement applicable to the genus as a whole". Particularly useful regulatory regions for expression in saliva are promoters that are active in cells of salivary glands ... particularly ... bovine ... Applicants' Specification pg 33 ln 7-13. The Applicant's teaching is supported by one having ordinary skill in the art stating that at the time of filing of the present invention the known genus of bovine salivary gland protein promoters was limited to the bSP30A and bSP30B promoters.

These arguments are not persuasive because as discussed above a transgenic caprine with the regulatory elements as described in the declaration is enabled but not a transgenic caprine lacking said salivary gland regulatory elements because this is an important point because the prior art has set forth that regulatory sequences of genes expressed in the cells of salivary gland are basically undeveloped and failed to direct high levels of polypeptide

expression. For example the limitations of using the "known" promoter sequence of the parotid secretory protein (PSP) gene the art provided an extensive review of the limitations of known salivary gland promoters. See throughout Samuelson. For example, the art teaches that parotid-specific transgene expression requires an upstream cis-regulatory domain, namely the parotid control region, and this parotid control region functions with a heterologous promoter and is indispensable for achieving transgene expression and deletion of specific regions results in ectopic gene expression and the inducible expression of the transgene expression in transgenic mice decreases over 30-fold. Note the specification points to the importance of the regulatory sequences besides the promoter for the claimed invention by emphasizing: "Among the sequences that regulate transcription that are useful in the invention, in addition to the promoter sequences discussed above, are enhancers, splice signals, transcription termination signals and polyadenylation sites, among others. Particularly useful regulatory sequences include those that increase the efficiency of expression of the polypeptide and/or protein of interest in transgenic organisms. Also particularly preferred in this regard are those that increase the specificity of expression in targeted compartments of a transgenic organism. Among highly particularly preferred regulatory regions in this regard are those that increase the efficiency, the specificity or both the efficiency and the specificity of expression in salivary glands, and the production of a desired substance thereby in the saliva of transgenic non-human animals in accordance with the invention." (see specification p 34-35). The guidance provided by the specification with respect to use of saliva specific regulatory elements was general and did not specifically relate to use of any particular regulatory sequence. Moreover, the specification while suggesting that certain regulatory elements (from PSP and B1-Ips genes) could be used failed to disclose the actual nucleotide sequences of such elements, which could direct a high level of transgene expression in saliva. This is an important point because the

prior art has set forth that regulatory sequences of genes expressed in the cells of salivary gland are basically undeveloped and failed to direct high levels of polypeptide expression. See Samuelson which discussed the limitations of using the "known" promoter sequence of the parotid secretory protein (PSP) gene. Also, Samuelson provided an extensive review of the limitations of known salivary gland promoters.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1, 6-13, 15-21, 23, 27-28 under 35 U.S.C. 103(a) as being unpatentable over Mikkelsen et al, (Nature 20(9): 2249-2255, 1992 (IDS)); Laursen J and Hjorth J P, (Gene 198(1-2): 367-72, 1997) in view of Golovan et al, Nat Biotechnol, 19(5):429-33, 2001; Golovan et al., (Nat Biotechnol, 19(8):741-5, 2001); Swenson and Reece (In: Dukes' Physiology of Domestic Animals, 11th Edition., Comstock Publishing Assoc. Ithaca, NY. pp 399-400, 1993); Lubon et al, (Transfusion Medicine Reviews X(2): 131-141, 1996); Lubon et al, (US. 5,880,327(IDS)); Coppes et al, (Radiation Research, 153: 339-346, 2000 (IDS)) is withdrawn in view of the amendment to a transgenic caprine.

The rejection of claims 29, 33-34 under 35 U.S.C. 103(a) as being unpatentable over Mikkelsen et al, (Nature 20(9): 2249-2255, 1992); Laursen J and Hjorth J P, (Gene 198(1-2): 367-72, 1997) in view of Golovan et al, Nat Biotechnol, 19(5):429-33, 2001; Golovan et al., (Nat Biotechnol, 19(8):741-5, 2001); Swenson and Reece (In: Dukes' Physiology of Domestic

Animals, 11th Edition., Comstock Publishing Assoc. Ithaca, NY. pp 399-400, 1993); Lubon et al, (Transfusion Medicine Reviews X(2): 131-141, 1996); Lubon et al, (US. 5,880,327); Coppes et al, (Radiation Research, 153: 339-346, 2000) and further in view of Deboer et al (6,140,552 (IDS)) is withdrawn in view of the amendment to a transgenic caprine.

Applicant's arguments are convincing in view of the amendment.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571)272-3305. The examiner can normally be reached on Monday through Friday from 9 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paras Peter can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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